ORIGINAL ARTICLE

Abnormalities of hemostasis predisposing to thrombosis in patients with end-stage renal disease awaiting transplantation

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To cite this article: M. Chekkal and al, Abnormalities of hemostasis predisposing to thrombosis in patients with end-stage renal disease awaiting transplantation. J Medical and Biological 2023; 1: 39-42

Summary

Kidney failure is a pathology that increases the risk of thromboembolic diseases. Thrombotic complications are particularly feared in renal transplantation and may be the cause of early graft loss. Especially since a link has been demonstrated between thrombophilia and acute or chronic transplant rejection. The stratification of patients according to their thrombotic risk before performing the transplant would make it possible to readjust the anticoagulant treatment.

Through a case-control study, we found that the levels of protein S and antithrombin in patients with end-stage renal disease (ESRD) were not lower compared to controls. On the other hand, the protein C level was significantly lower in the patients but by applying the Chi-2 test we did not find a statistically significant relationship between the protein C deficiency and the ESRD (P=0.114).

Also, 25% of the patients had lupus anticoagulants Vs only 1.19% of the controls. A significant statistical relationship was found between their presence and the disease (P=0.000).

In conclusion, we did not find any added risk of deficiency in physiological coagulation inhibitors or resistance to activated protein C in ESRD. However, the realization of these examinations remains

obligatory in order to evaluate the thrombotic risk before kidney transplant both in the donor and the recipient. Lupus anticoagulants represented the hemostasis anomaly most associated with ESRD and would therefore deserve our interest for further studies.

Keywords: Chronic Renal Disease- thrombosis- Lupus Anticoagulants- physiological inhibitors of the coagulation- V Leiden mutation

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- **Article received: 01/03/2023**
- **Article accepted: 06/03/2023**

Funding

The authors received no financial support for their research, participation and/or publication of this article.

Conflicts of interest

The authors declare that they have no conflict of interest

Introduction:

Kidney failure is a pathology that increases the risk of thromboembolic diseases [1-2-3]. The death rate from pulmonary embolism is higher in patients with renal impairment than in those without [4-5].

Also, the thrombotic risk is twice as high in patients with advanced chronic renal disease (CKD) compared to early stages of the disease [6-7] and this risk begins to increase when glomerular filtration decreases to less than 75 ml /min/1.73m2 [8].

In patients with renal insufficiency, thrombosis takes different forms such as deep vein thrombosis (DVT) with or without pulmonary embolism, thrombosis of arteriovenous fistulas and those on central catheter. In addition, thrombus formation can also occur in arteries and could present as acute coronary syndrome, stroke, or peripheral arterial occlusion [3].

Thrombotic complications are particularly feared in renal transplantation since they can be the cause of early graft loss [9]. Especially since several studies have described the link between the acquired or constitutional state of thrombophilia and acute or chronic transplant rejection.

Therefore, the stratification of patients according to their thrombotic risk before performing the transplant will make it possible to readjust the anticoagulant treatment.

The objective of our work was to look for abnormalities of hemostasis predisposing to thrombosis in patients with end-stage renal disease (ESRD) awaiting renal transplant.

Patients and methods

Patients were recruited through the renal transplant program. We included in our study patients aged 16 years and over with end-stage renal disese awaiting a transplant.

Patients with a personal history of thrombosis and those on current anticoagulant therapy were excluded. Two 5 ml

samples of venous blood were collected in a tube containing citrate as an anticoagulant according to the general recommendations applying to current hemostasis tests [10]. We used healthy kidney donors as a control population.

End-stage chronic renal disease was defined by a glomerular filtration rate below 15 ml/min/1.73 m2 calculated by the MDRD (Modification in Diet in Renal Disease) formula. All patients were candidates for living donor kidney transplantation.

The dosage of antithrombin and protein C were carried out by determining the activity by colorimetric method using Stago® reagents, while the determination of the activity of protein S was made by chronometric method using the same range of reagents. Screening for the V Leiden mutation was done by the activated protein C resistance test (APCR) and the search for lupus anticoagulants (LA) by the diluted Russel's viper venom time (DRVVt). For each series of assays we used a normal internal quality control and another pathological. All the assays were carried out on a coagulation machine of the STA Compact Max® type (Stago®, France). The level of physiological coagulation inhibitors was expressed as a percentage relative to their levels in the calibration plasma. APCR and lupus anticoagulants were expressed as positive or negative results relative to a validation threshold

For the comparison of the levels of physiological inhibitors of coagulation between the patients and the controls we carried out a Student's test. The statistical relationship between the inhibitor deficiency and the ESRD was sought by a Chi-square test. The significant statistical difference was considered for a value $P<0.05$. For all our calculations we used SPSS software version 17.

Results

80 patients were eligible and 84 controls. The baseline characteristics of the study population and the description of hemostasis abnormalities

	Patients (n=80)	Controls (n=84)	P
Age (median [Q1-Q3])	30[24,75-37,25]	47[37,5-55]	
Sexe (H/F)	41/39	32/52	
Protein C (mean+/- SD)	95.45±19,38	113,44±22,78	0,000
Protein S (mean+/- SD)	93,77±25,38	93,77±25,95	1,000 (N.S)
Antithrombin (mean+/- SD)	105,60±13,61	103,40±11,03	0,355 (N.S)
APCR (% of positives)	5	5,95	1,000 (N.S)
LA (% of positives)	25	1,19	0,000
[Q1-Q3] : interquartile range. SD : standard deviation. APCR : activated protein C resistance. LA : lupus anticoagulants. NS : not significative			

Table 1: Basic characteristics and distribution of hemostasis abnormalities predisposing to thrombosis in the population studied

predisposing to observed thrombosis are given in Table 1. We found that protein S and antithrombin levels were not significantly different between the patients population and that of controls when the Student test was applied.

On the other hand, the protein C level was significantly lower in the patients but by applying the Chi-2 test we did not find a statistically significant relationship between the protein C deficiency and the ESRD (P=0.114).

The V Leiden mutation detected by the APCR test did not have a significant statistical relationship either with ESRD.

25% of patients with ESRD had lupus anticoagulants Vs only 1.19% of controls. A significant statistical relationship was found between their presence and the disease (P=0.000).

Discussion

The data in the literature on the presence or absence of a deficiency in physiological coagulation inhibitors in end-stage renal disease are very contradictory.

Our results agree in more ways than one with those of Heidenreich *et al* who found no cases of physiological coagulation inhibitor deficiency in 165 patients studied before undergoing a kidney transplant[11].

Other studies like that of Ghisdal *et al* [12] have found a state of thrombophilia with a deficit of physiological coagulation inhibitors to varying degrees in patients with ESRD. Of the 215 patients studied, 12.1% had protein C deficiency, 5.8% protein S deficiency and 17.4% antithrombin deficiency and all these abnormalities disappeared after kidney transplantation proving that it is acted of a state of acquired thrombophilia and not constitutional one.

The absence of a deficiency in physiological inhibitors of coagulation does not eliminate the existence of a state of hypercoagulability widely recognized today in ESRD. Other stakeholders can explain this state of hypercoagulability such as microparticles [13-14]. These are small membrane sacs that can be shed from variable cells like endothelial cells, platelets, monocytes, and macrophages. Their procoagulant effect is the product of the presence on their surfaces of procoagulant phospholipids and of tissue factor which initiates coagulation and increases the generation of thrombin [15-16]. They are used now as markers of hypercoagulability in various pathologies such as CKD and cancers. They have been found to increase the predictive power of VTE in cancer [17].

APCR was present similarly between patients (5%) and controls (5.95%). Its molecular equivalent, the V Leiden mutation is present according to some studies in 1.3 to 2% of the healthy Algerian population [18-19].

Lupus anticoagulants have been the most linked to ESRD. Thus, in a large meta-analysis conducted by Paul et al [20] the prevalence of lupus anticoagulants was 8.7% in patients Vs 0.2% in controls. The authors also found that the prevalence of lupus anticoagulants was greater in patients with fistula occlusion compared to that in patients without occlusion (23% vs 0.3%).

Canaud *et al* found that the presence of lupus anticoagulants before transplantation was correlated with renal vessel thrombosis and with recurrence of antiphospholipid syndrome nephropathy after transplantation and suggested that the preventive strategies with plasmapheresis and/or rituximab could be useful in these particular cases of transplants [21].

Conclusion

We did not find any added risk of physiological coagulation inhibitor deficiency in ESRD or resistance to activated protein C, the molecular equivalent of which is the V Leiden mutation.

However, the realization of these examinations remains obligatory in order to evaluate the thrombotic risk before kidney transplant both in the donor and the recipient. It should even be extended to the study by molecular biology of the heterozygous or homozygous state of the V Leiden mutation and the G20210A mutation of the prothrombin gene which remain by far the most frequent abnormalities of constitutional hemostasis predisposing to thrombosis. .

Lupus anticoagulants represented the hemostasis anomaly most associated with ESRD and deserve our interest for further studies on their association with post-transplant thrombosis and ways to prevent it.

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